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Paraneoplastic Pemphigus in a Patient With Non-Hodgkin's Lymphoma

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Paraneoplastic pemphigus (PNP) is an autoimmune disorder occurring in the setting of an underlying neoplasm in which patients have polymorphous skin and mucous membrane lesions.

We describe a patient with non-Hodgkin's lymphoma who developed bullous, ulcerating lesions in an area being treated with radiation therapy. The diagnosis of PNP was confirmed by indirect immunofluorescence of the patient's serum on rat bladder. The disorder was refractory to therapy, and ultimately the patient expired. © 1996 Wiley-Liss, Inc.

Key words: skin lesion, bullous pemphigus

INTRODUCTION

Paraneoplastic pemphigus (PNP) is a rare entity that has been characterized by Anhalt [1]. Patients with an associated neoplasm develop painful extensive skin and mucosal ulceration that is usually resistant to therapy, although long-term survivors have been reported [2].

CASE REPORT

This patient was a 66-year-old white man with a long history of non-Hodgkin's lymphoma. He was treated with chemotherapy (cyclophosphamide, Adriamycin, vincristine, prednisone-BCG, and then cyclophosphamide, vincristine, prednisone) until remission was attained. Sixteen years later, he developed a right axillary mass. A biopsy revealed a nodular mixed lymphoma, and treatment with chlorambucil was initiated.

In April of 1992, he was diagnosed with Guillain-Barré syndrome and underwent plasmapheresis with recovery. Chlorambucil was resumed. In February of 1993, he developed herpes zoster and was treated with acyclovir. When a marked increase in right axillary adenopathy was noted, chlorambucil was discontinued and radiation therapy instituted (right axillary, supraclavicular, and cervical regions). The axillary mass partially responded.

Two weeks after radiation, he developed an erythematous, papular rash in the distribution of the radiation field measuring 6 × 7 cm. One week later, the skin over the right breast (outside the radiation field) had become erythematous. He was treated with doxycycline for cellulitis, and when the lesions progressed, cefaclor was prescribed. Several days later, painful, vesicular lesions of the oral mucosa and lips developed. Acyclovir was administered for presumed herpes. Subsequently, the patient's rash progressed to the arms and legs and became vesicular with bleeding, necessitating hospitalization for IV acyclovir. The possibility of a drug reaction was considered, and steroids were implemented (60 mg/day).

In the hospital, skin cultures grew *Staphylococcus*, (coagulase negative), and viral/fungal cultures were negative. A skin biopsy showed interface dermatitis consistent with erythema multiforme.

Laboratory tests showed a normal hemogram, erythrocyte sedimentation rate, and rheumatoid factor titer and negative cryoglobulins. Immunoglobulin levels were normal, with a mild decrease in IgA. CH_{50} and C_4 were normal with, a small decrease in C_3 at 78 mg/dl (normal, 85–180 mg/dl). Antinuclear antibody titer was 1:320 with an atypical speckled pattern and an atypical non-antinuclear antibody pattern.

The skin lesions markedly progressed on steroid ther-

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Fig. 1. Paraneoplastic pemphigus: diffuse, ulcerated areas on trunk and arms.

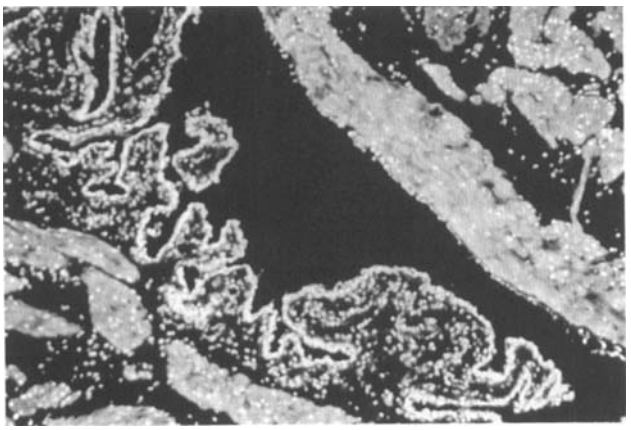

Fig. 2. Definitive diagnostic test for paraneoplastic pemphigus: positive indirect immunofluorescence on rat bladder.

apy, leaving large blistered areas involving the head, face, trunk, upper arms, buttocks, and posterior thighs (Fig. 1). Repeat skin biopsies were done. Microscopic examination and immunofluorescent staining were consistent with pemphigus. The history of lymphoma, extensive mucosal involvement, immunofluorescent staining, and poor response to steroids suggested a diagnosis of PNP. A sample of the patient's plasma was sent for indirect immunofluorescence (IIF) testing on rat bladder (diagnosis was confirmed post mortem; Fig. 2). The patient was plasmapheresed daily and started on Imuran. Unfortunately, the disease progressed, and he expired approximately 1 month after admission.

At autopsy, diffuse epidermal blistering and sloughing was noted involving virtually his entire body. Histologically, the skin revealed interface dermatitis, a pattern consistent with pemphigus vulgaris. The right axillary node measured 7 × 7 cm and revealed non-Hodgkin's lymphoma, small cleaved.

DISCUSSION

The diagnosis of PNP was confirmed by IIF on rat bladder epithelium. The diagnosis can also be made with immunoprecipitation showing autoantibodies reactive with Desmoplakin 1 (250 kd), the bullous pemphigoid antigen (230 kd), Desmoplakin II (210 kd), and a 190 kd protein. IIF on rat bladder has now been shown to be a highly specific test for PNP and is easily performed [3].

The most common neoplasm associated with PPN is non-Hodgkin's lymphoma. Other neoplasms associated with PNP include chronic lymphocytic leukemia, benign thymoma, sarcoma, Waldenström's macroglobulinemia, and bronchogenic squamous cell carcinoma [2].

Clinically, PNP mimics erythema multiforme. Oral mucosal involvement is usually severe. Vesicles and bullae may be extensive. Ocular and conjunctival involvement is common. Ulcerations of the trachea, pulmonary parenchyma, myocardium, urethra, and esophagus have been reported [4].

As with other reports of PNP, this patient's presentation was similar to erythema multiforme. Our case was unusual in that there has only been one other case published in which PNP began in an area of radiation therapy [4].

Treatment for PNP is rarely successful. Immunosuppressive agents have included steroids, azathioprine, and methotrexate. Our patient was treated with plasmapheresis, prednisone, and azathioprine without improvement. In a case of chronic lymphocytic leukemia, marked improvement was noted with prednisone 35 mg/day and cyclosporine 5 mg/kg/day [2]. Another patient with non-Hodgkin's lymphoma and PNP was treated with prednisone 40 mg and azathioprine 100 mg/day with clearing of the lesions [5].

It is not known if timing of immunosuppression in PNP is important. If this syndrome is recognized and treatment begun early, patient outcome may possibly improve.

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